

NATIONAL PBM COMMUNICATION • July 2, 2009

Varenicline (Chantix®) and Bupropion (Zyban®, Wellbutrin®, and generics) and Neuropsychiatric Events

- The Food and Drug Administration (FDA) has continued to receive post-marketing reports of mood and behavioral changes temporally associated with the use of varenicline (Chantix) and bupropion (Zyban and generics) for smoking cessation.^{1,2}
- FDA has required the manufacturers of these medications to add new *Boxed Warnings* and develop patient Medication Guides that delineate the risk of the above neuropsychiatric symptoms.
- These warnings with varenicline have been known to VA, and are consistent with current VA prescribing criteria. (For further guidance on varenicline, please refer to the PBM-MAP Criteria for Use for Varenicline at <http://www.pbm.va.gov/default.aspx>.)
- The warning with bupropion is not new and holds true for all antidepressants as well.
- Neuropsychiatric events reported to the FDA in patients taking varenicline (Chantix) and bupropion (Zyban and generics) include^{1,2}:
 - Changes in behavior
 - Hostility
 - Agitation
 - Depressed mood
 - Suicidal thinking and behavior
 - Attempted suicide
- FDA recommends^{1,2}:
 - *Healthcare professionals should advise patients to stop taking varenicline or bupropion and contact a healthcare provider immediately if they experience agitation, depressed mood, and any changes in behavior that are not typical of nicotine withdrawal, or if they experience suicidal thoughts or behavior.*
 - *If varenicline or bupropion is stopped due to neuropsychiatric symptoms, patients should be monitored until the symptoms resolve.*
 - *Family members and caregivers should also be alerted to the potential for changes in mood or behavior and contact the health care provider if they observe these changes in the person taking varenicline or bupropion.*
- VA Center for Medication Safety (VAMedSAFE) has been monitoring and analyzing reports of adverse events with varenicline (Chantix) and bupropion (Zyban and generics) since 2007 to better characterize the adverse event profile in the veteran population.
- Providers should document/report all possible adverse events related to varenicline and bupropion as per the usual protocols used at their VA and continue to use these medications according to VA criteria.
- Providers interested in additional information please see attachment.
- For information, contact Mark Geraci, Pharm.D., BCOP, at Mark.Geraci@va.gov.

ACTIONS

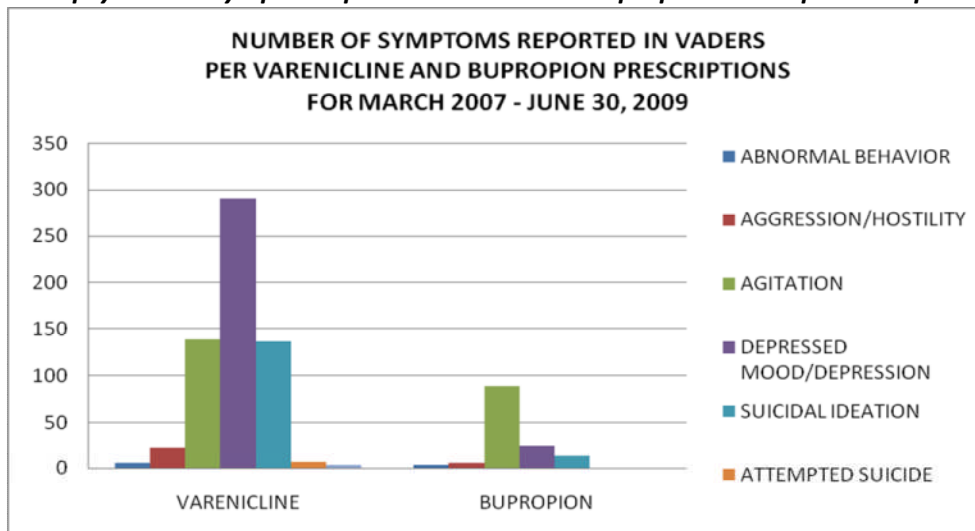
- **Facility Director (or physician designee):** Report completion of actions to the VISN Director.
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe/use/handle this agent (e.g., **primary care providers, mental health providers, psychiatrists, and smoking cessation specialists**, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate. Report completion of actions to the Facility Director.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).
- **VISN Directors:** Within 10 business days of receipt (due 07/17/2009), communicate to PBM/VAMedSAFE that all actions have been completed via the Feedback tool: http://vaww.national.cmop.va.gov/PBM/visn_drug_recalls_alerts/default.aspx.

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- Literature has addressed suicidality with varenicline (Chantix) and bupropion (Zyban and generics)^{3, 4, 5, 6}
 - One study evaluated the serious adverse reactions of bupropion for smoking cessation from 2001 to 2004 using the French Pharmacovigilance Database.³
 - Bupropion was prescribed to nearly seven hundred thousand patients during the first 3 years of marketing in France.
 - 1682 cases of adverse reactions were reported (22.5 % were serious neurological reactions).
 - 17.3% of the serious neuropsychiatric adverse events reported suicide attempts/suicides.
 - Risk factors (history of depression, suicide attempts, etc.) were described for 66% of patients experiencing these events.
 - A Cochrane Review stated that increased risk of suicide with bupropion remains unproven.⁴
 - A prescription-event monitoring study which looked at the safety and drug utilization profile of varenicline used in general practice in England reported 2 cases of attempted suicide/suicide out of 2682 patients.⁵
 - Both patients had previous history of psychiatric illness and precipitating factors for the event.
 - One case report describes the completed suicide of a 39-year old man in France who was taking varenicline.⁶
- Within the VA, there were a total of 238, 826 prescriptions for varenicline (100, 706 unique patients) and a total of 2, 145, 152 prescriptions for bupropion (368,340 unique patients) between March 2007 and May 31, 2009. From March 2007 and June 30, 2009, VA providers submitted 1493 adverse event reports (with 2298 symptoms) on varenicline and 898 adverse event reports (with 1329 symptoms) on bupropion. For varenicline, there were 1349 psychiatric disorders reported (149 cases of suicidal and self-injurious behaviors) and for bupropion, there were 420 psychiatric disorders reported (13 cases of suicidal and self-injurious behaviors).

Number of Neuropsychiatric Symptoms per Varenicline and Bupropion Prescriptions Reported to VADERS



REFERENCES:

1. FDA Public Health Advisory. <http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm169988.htm> (Accessed July 1, 2009).
2. FDA Information for Healthcare Professionals. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm169986.htm> (Accessed July 1, 2009).
3. Bevens MN, Guy C, Mounier G, Laporte S, Ollagnier M. Serious adverse reactions of bupropion for smoking cessation: analysis of the French Pharmacovigilance Database from 2001 to 2004. *Drug Saf.* 2008; 31(11): 1017-26.
4. Hughes J, Stead L, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Review.* 2007 Jan 24; (1): CD000031.
5. Kasliwal R, Wilton LV, Shakir SA. Safety and drug utilization profile of varenicline as used in general practice in England: interim results from a prescription-event monitoring study. *Drug Saf.* 2009; 32(6): 499-507.
6. Kintz P, Evans J, Villain M, Cirimele V. Smoking cessation with varenicline: a suicidal fatality. *J Anal Toxicol.* 2009 Mar;33(2):118-20.